REMARKS

1. Status of claims

After entry of the above amendment, claims 1-8, 18-23, 26, 28-29, and 33-40 are pending.

2. Support for amendment

The amendment of claim 28 finds support in Figures 15A-15B and clarifies its dependence on claim 1. The amendment of claims 1, 5, 7, and 37 finds support at p. 4, line 32 to p. 5, line 1. No new matter has been added by this amendment.

3. Claim rejections under 35 U.S.C. § 112

The Examiner rejected claim 8 under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. Specifically, the Examiner alleged the specification failed to teach how to "derive" at least one growth factor from bovine bone. Applicants traverse this rejection.

Applicants point to the specification at p. 5, lines 4-24 and p. 9, lines 24-26, and US Pats. Nos. 5,290,763; 5,731,191; and 5,563,124, referred to at p. 9, lines 24-26, as providing the skilled artisan with teachings as to how to derive at least one growth factor from bovine bone. Therefore, Applicants request this rejection of claim 8 be withdrawn.

The Examiner rejected claims 1-8, 18-23, 26, 28-29, and 33-40 under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement for skin wound healing in non-mice species, such as humans. Applicants traverse this rejection.

Examples 1-3 of the present specification (pp. 9-14) followed protocols described by Cooper *et al.*, *Prog. Clin. Biol. Res.* (1991) 365:429-42. A copy of Cooper *et al.* is attached for

the Examiner's convenience. Cooper *et al.* indicates mice were known to the ordinary skilled artisan as models for human skin applications. Also, Applicants point to Example 3 of the present specification, which uses the mouse model to compare the claimed compositions with Regranex®, a product previously approved by the FDA for treatment of wounds in humans. The claimed composition proved to be at least as effective as Regranex® in wound healing in the mouse model (p. 14, Table 4 and lines 6-9). Taken together, these observations provide guidance to the skilled artisan to practice the claimed invention in non-mouse species, such as humans, without undue experimentation. Therefore, Applicants request this rejection of claims 1-8, 18-23, 26, 28-29, and 33-40 be withdrawn.

The Examiner rejected claim 8 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Specifically, the Examiner alleged the specification failed to define the term "derive." Applicants traverse this rejection.

Applicants point to the specification at p. 5, lines 4-24 and p. 9, lines 24-26, and US Pats. Nos. 5,290,763; 5,371,191; and 5,563,124, referred to at p. 9, lines 24-26, as providing the skilled artisan with guidance as to how the term "derive" is used in the present claims. Therefore, Applicants request this rejection of claim 8 be withdrawn.

The Examiner rejected claims 1-5, 6-8, 18-23, 26, 28-29, and 33-40 under 35 U.S.C. § 112, second paragraph, for allegedly being incomplete. Specifically, the Examiner alleged essential method steps relating to how to apply the mixture to a skin wound were omitted. Applicants traverse this rejection.

Applicants point to multiple passages in the specification as teaching how to apply the claimed composition to a skin wound. These include p. 15, lines 10-15; p. 9, line 26 to p. 10, line 2; Example 2, pp. 11-12; p. 12, lines 6-10; and Regranex® full prescribing information cited

at p. 12, a copy of which is enclosed for the Examiner's convenience. Applicants submit the skilled artisan having the benefit of the present specification would readily determine how to apply the claimed mixture. Therefore, Applicants request this rejection of claims 1-5, 6-8, 18-23, 26, 28-29, and 33-40 be withdrawn.

The Examiner rejected claims 1-8, 28-29, and 33-40 under 35 U.S.C. § 112, second paragraph, for allegedly being incomplete. Specifically, the Examiner alleged essential method steps relating to the method of depleting histones and/or ribosomes were missing. In light of the above amendment, Applicants traverse this rejection.

The present specification guides the skilled artisan regarding techniques for depleting histones and/or ribosomes at p. 7, lines 4-10 and p. 16, line 32 to p. 17, line 4. Immunoaffinity chromatography is mentioned as a particular (but not limiting) example. It should be noted the plain meaning of "depleting histones and/or ribosomes" encompasses situations in which *at least some, but not necessarily all*, histones and ribosomal proteins are excluded from the mixture. Therefore, some histones and/or ribosomal proteins can be present in the mixture. For at least these reasons, Applicants request this rejection of claims 1-8, 28-29, and 33-40 be withdrawn.

The Examiner rejected claims 1-5, 7-8, 28-29, and 33-40 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Specifically, the Examiner alleged the terms "depleted", "free", "substantially free", and "removed" were not defined or described in the specification.

In light of the above amendment, these terms have been replaced with the term "excluded", which is defined in the specification at p. 4, line 32 to p. 5, line 1. Therefore, Applicants submit these claims are not indefinite and request this rejection of claims 1-5, 7-8, 28-29, and 33-40 be withdrawn.

The Examiner rejected claim 28 under 35 U.S.C. § 112, second paragraph, as being indefinite for reciting limitations excluded by its parent claim, claim 1. Applicants respectfully traverse this rejection.

Claim 1 recites a method comprising applying a composition "from which histones and/or ribosomes are excluded." The plain meaning of this phrase encompasses situations in which *at least some, but not necessarily all*, histones and ribosomal proteins are excluded from the mixture. Therefore, some histones and/or ribosomal proteins can be present in the mixture and remain within the scope of claim 1. No improper dependence of claim 28 on claim 1 occurred, and therefore Applicants request this rejection of claim 28 be withdrawn.

The Examiner also rejected claim 28 under 35 U.S.C. § 112, second paragraph, as being indefinite, specifically for reciting amino acid sequences. Applicants traverse this rejection.

Figures 15A-15B show sequence data determined by amino acid sequencing of tryptic fragments ("Sequence Data") along with the best match found for each fragment sequence in a database taken from various proteins from various species (p. 16, lines 5-11). The sequences identified in claim 28 by SEQ ID NO correspond to the Sequence Data column in Figures 15A-15B. The "Best Database Match" sequences represent the best matches found in the database at the time the match was performed. There is no lack of clarity about which species the sequences identified by SEQ ID NO are derived from, see Example 5, pp. 15ff. As for the alleged lack of clarity regarding parenthetical amino acids, Applicants submit claim 28, as amended, recites all alternatives listed in Figures 15A-15B separately, with distinct SEQ ID NOs for each sequence, and therefore claim 28 is definite.

4. Claim rejections under 35 U.S.C. § 103

The Examiner rejected claims 18-23 under 35 U.S.C. § 103(a) as being unpatentable over Wang *et al.*, US 6177406 ("Wang"), in view of Cerletti *et al.*, EP 0433225 A1 ("Cerletti") and Stelnicki *et al.*, Plast. Reconstr. Surg. (1998) 101:12-19 ("Stelnicki"). Specifically, the Examiner alleged Wang taught the use of bovine-derived BMP-3 to treat burns and incisions; Cerletti taught the use of TGF-βs to treat burns and incisions; and Stelnicki taught the use of BMP-2 to treat incisions. Applicants traverse this rejection.

First, the references, alone or in any combination, do not teach or suggest a bone-derived composition comprising all of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, TGF-β1, TGF-β2, TGF-β3 and FGF-1. The references separately teach the use of BMP-3, TGF-β1, TGF-β2, TGF-β3, and BMP-3, but do not teach any of the other components. Also, the references teach preparation of the BMP or TGF-β from either recombinant host cells in culture (Wang and Cerletti) or isolation from human fetal skin (Stelnicki). The references therefore do not guide the skilled artisan to consider a bone-derived composition comprising all of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, TGF-β1, TGF-β2, TGF-β3 and FGF-1, and claims 18-23 are patentable over the references for that reason.

Further, claim 20 recites a method wherein the proteins are at least partially phosphorylated and glycosylated. Wang, Cerletti, and Stelnicki provide no teaching that native post-translational phosphorylation and glycosolation of the proteins they worked with is desirable or useful and that purification of the proteins should be undertaken with maintenance of post-translational modification. Cerletti in fact teaches denaturation and renaturation of TGF-β [0012]. Wang indicates disruption of glycosylation sites in engineered BMP-3 is acceptable (col. 2, lines 56-62). Both Wang and Cerletti teach the use of microbial host cells, including

prokaryotic host cells, for protein production, without addressing possible derangements of normal phosphorylation or glycosylation that may arise from production in microbes, including prokaryotes.

For at least the foregoing reasons, Applicants request this rejection of claims 18-23 be withdrawn.

5. Request for clarification

The Office Action Summary indicated that the drawings filed on November 4, 2004 were objected to by the Examiner. However, there is no statement of which drawing was objected to. If the Examiner intended to object to Figure 15A for its alleged lack of clarity, Applicants point to their discussion above traversing the rejections of claim 28 under 35 U.S.C. § 112. Applicants submit Figure 15A is clear and definite. If the Examiner did not intend to object to Figure 15A, Applicants request clarification.

6. Conclusion

Applicants submit all pending claims are in condition for allowance. The Examiner is invited to contact the undersigned patent agent at (713) 934-4065 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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December 19, 2005

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